Undersea Biomedical Research, Vol. 13, No. 3, September 1986

Effects of ethanol and amphetamine on inert gas narcosis in humans

B. FOWLER, K. HAMILTON, and G. PORLIER

Departments of Physical Education and Psychology, York University, 4700 Keele Street, Downsview, Ontario, M3J 1P3, Canada; and Defence and Civil Institute of Environmental Medicine, PO Box 2000, Downsview, Ontario, M3M 3B9, Canada

Fowler B, Hamilton K, Porlier G. Effects of ethanol and amphetamine on inert gas narcosis in humans. Undersea Biomed Res 1986; 13(3):345–354.—The effects of ethyl alcohol (1 ml/kg body weight), dextroamphetamine (15 mg), and nitrous oxide (20%) on reaction time were investigated in 6 subjects with a 2-, 3-, and 4-choice serial reaction time task. Each drug was assessed separately and in combination with nitrous oxide. The error rate was held constant. Neither ethanol and nitrous oxide nor amphetamine and nitrous oxide influenced the slope of the Hick-Hyman function, but the former combination increased the intercept while the latter decreased it. The drugs, either alone or in combination, shifted the frequency distributions of the reaction times as a whole, rather than modifying either their shapes or the pattern of the response latencies around an error. These results indicate that the drugs have a common pattern of effects on reaction time and that alcohol exacerbates narcosis while amphetamine ameliorates it. This is interpreted as support for the view that narcosis causes a nonspecific slowing of information processing by decreasing arousal.

narcosis
nitrous oxide
ethanol
amphetamine
choice reaction time

Inert gas narcosis degrades human performance on a variety of tasks by increasing time to respond and decreasing accuracy of responding (1). Recently, the slowed processing model has been proposed to account for these effects (2, 3). The model postulates that, to a large extent, narcosis can be explained by a single fundamental deficit—the slowing of information processing. This slowing is reflected by increases in reaction time. Decreases in accuracy are regarded as strategic effects which are not a necessary concomitant of narcosis. A detailed review of these arguments can be found elsewhere (4).

The question arises of how to explain slowing which cannot be isolated to a particular part of the information processing system. One possibility is that narcosis decreases arousal. The concept of arousal refers to the level of excitation in the CNS and its relationship to behavior (5, 6). There is evidence that, in humans, low-to-

moderate levels of arousal are positively correlated with performance efficiency on a number of tasks (7). One way to investigate this hypothesis is to manipulate the level of arousal under narcosis and determine how processing is affected.

Ethanol is considered to be a CNS depressant and, like narcosis, is known to increase reaction time (8). On the other hand, amphetamine is regarded as an excitant, although its effects on reaction time are not as clear. With alert, nonfatigued performers, some studies have found decreases in reaction time but others have found no change, although amphetamine appears to stave off increases in reaction time under conditions of drowsiness or fatigue (9). On the assumption that these drugs influence arousal in opposite directions, the foregoing argument leads to the prediction that ethanol should exacerbate narcosis and amphetamine should ameliorate it. The primary purpose of the present experiment was to test this hypothesis using a serial choice reaction time task (SCRT). A second purpose of this study was to examine the effects of narcosis on reaction time independent of movement time. In a previous study, narcosis was analyzed with a version of the SCRT in which reaction time and movement time were confounded (3). By comparing the pattern of results from both versions of the SCRT, the effects of narcosis on reaction time and movement time can be separated.

METHODS

Subjects

Four female and 2 male university students (20–25 yr old) volunteered for this experiment and were paid for their participation. Each subject was medically screened and signed informed-consent documents. All were social drinkers and had experienced the effects of breathing nitrous oxide. As part of the screening procedure, they also experienced a 5-mg dose of dexamphetamine. The experimental protocol was approved by Human Ethics Committees at both York University and DCIEM.

Apparatus

The SCRT consisted of five push-buttons (Microswitch, model PK85022) mounted on a console in a semicircular fashion so that they could be operated by resting a finger on each one. The buttons were individually adjustable in the horizontal plane to accommodate different hand sizes and finger combinations. The stimulus for depressing a button was a red-light-emitting diode (LED, Fairchild model FLV560) mounted immediately in front of it. A PDP 11/04 computer controlled a sequence of events in which an LED was randomly illuminated until the appropriate button was depressed, this simultaneously turned off the LED and randomly illuminated another one. The computer recorded both the time interval between the illumination of each LED and depression of the corresponding button, as well as the number of errors (depressing an unlit button).

Inert gas narcosis was induced by breathing a 20% N_2O:80% O_2 mixture with air as a control via a nonrebreathing oral-nasal mask. Ethyl alcohol (40% by volume) was administered orally using a dose of 1.0 ml/kg of body weight mixed with orange juice to a total volume of 350 ml. The control consisted of an equivalent volume of

juice with 1 ml of ethanol layered on top. A fixed dose of 15 mg of dextroamphetamine sulfate (Dexadrine®) was administered orally in three capsules with dextrose in identical capsules as a control.

Design

A repeated measures, single blind design was used comprising 12 separate sessions with numbers 1, 5, 8, and 12 as placebo conditions. Nitrous oxide, ethanol, or amphetamine were administered singly in sessions 2, 3, and 4 and again in sessions 9, 10, and 11. In sessions 6 and 7, nitrous oxide was combined with ethanol in one instance and with amphetamine in the other. The order of administration of the drugs was counterbalanced between subjects and was different for each one in the single drug conditions. In each session, 2-, 3-, and 4-choice stimulus-response combinations were given once. The order of administration was randomized between subjects and within a subject across sessions.

Procedure

The task was to continuously extinguish each lighted LED as quickly as possible by depressing the appropriate button while maintaining an error rate of 5 ± 1.5%. Before the experiment, the subjects were trained without drugs on each choice condition until their performance was relatively stable. The fingers used during the 2-choice condition were the index and middle fingers of the preferred hand and the index finger of the nonpreferred hand. The index and middle fingers of both hands were used in the 3-choice condition, and the thumb of the preferred hand was added in the 4-choice condition. These combinations were chosen to minimize response variability on the basis of a pilot study.

In the experiment, the subjects were tested individually while seated with the SCRT console in front of them at about knee height, so that their fingers could rest comfortably on the buttons. Each choice condition was performed for 90 s and these data were used for analysis if an error criterion of 5 ± 1.5% was met. If not, the data were discarded and the run repeated. Sessions were held in the afternoon, at least 1, and no more than 5 d apart. The subjects were only allowed a bowl of soup for lunch. The capsules were ingested 2 h before each session, and the liquid 35 min before, over a 5 min period. Breathing via the oral-nasal mask commenced 10 min before testing and continued throughout the session. These time intervals were chosen so that the effects of ethanol and amphetamine would be at their peak during the testing period.

RESULTS

An inspection of the error rates for individual sessions indicated that the 5 ± 1.5% criterion had been maintained. These rates are summarized in Table 1 for the pooled placebo, the pooled single drug, and the combined drug conditions. A repeated measures analysis of variance on these data was not significant (5, 25 = < 1) confirming that the error rate did not differ between conditions.

TABLE 1
MEAN PERCENTAGE ERROR RATES FOR THE SERIAL CHOICE REACTION TIME TASK

Pooled Conditions				N_2O + Alcohol	N_2O + Amphetamine
Control	N_2O	Alcohol	Amphetamine		
4.3 ± 0.2*	4.4 ± 0.1	4.5 ± 0.3	4.5 ± 0.3	4.4 ± 0.2	4.8 ± 0.5

*SEM. N_2O = nitrous oxide.

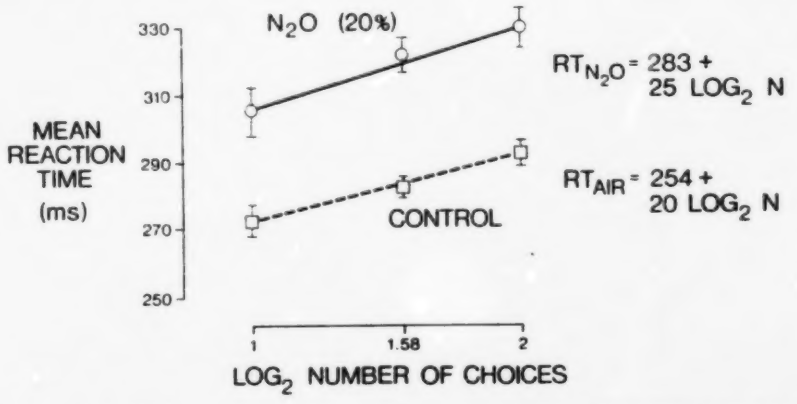

Fig. 1. Relationship between reaction time and $\log_2 n$ where n = number of choices (Hick-Hyman Law) for the first placebo and N_2O conditions. Linear functions were fitted by regression analysis and are based on six subjects. *Bars* represent SEM.

The Hick-Hyman Law states that choice reaction time can be represented by $a + b \log_2 n$, where a and b are the intercept and slope, respectively, of a linear function and n = number of stimulus-response choices (10). It was verified that the data from this experiment could be analyzed in these terms by plotting latency for correct first responses (omitting errors and the subsequent error-correcting response) as a function of $\log_2 n$ separately for all subjects and conditions.

An example of this, summed across subjects, for both the first control and the first nitrous oxide condition is illustrated in Fig. 1. Using the method of least squares for linear regression, a, the intercept, and b, the slope, of the Hick-Hyman function were calculated for each subject in every session. The analyses described below are based on these data.

To determine whether the 4 placebo conditions differed from one another, a one-way analysis of variance was performed separately on the values of a and b. Neither one was significant (F 3, 15 = < 1 and F 3, 15 = 3.19, respectively). Therefore, the placebo conditions were pooled for further analyses. To compare the single drug conditions, a two-way analysis of variance, consisting of 3 drugs × 2 sessions (2, 3, 4 vs. 9, 10, 22) was conducted separately on the values of a and b. For b, no effects were significant. For a, drugs (F 2, 10 = 14.4, $P < 0.01$) and sessions (F 1, 5 = 185.1, $P < 0.001$) were significant, but not the interaction between them. With respect to

the sessions effect, these results indicate that *a* decreased from sessions 2, 3, and 4 to sessions 9, 10, and 22 (272 vs. 256 ms, respectively) by the same amount for each drug. A Duncan post hoc test on the drug effect revealed that *a* was lower for amphetamine (251 ms) compared to either nitrous oxide (274 ms, $P < 0.01$) or ethanol (266 ms, $P < 0.01$). However, nitrous oxide and ethanol were not different from one another.

Since the improvement in *a* between the single drug conditions was the same for each drug, these conditions were pooled for the purposes of comparison with the combined drug conditions. One-way analyses of variance were then conducted separately on the values of *a* and *b* of the pooled placebo, the three pooled single drug, and the two combined drug conditions. There was no significant difference for *b* (F 5, 25 = < 1) but there was a significant effect for *a* (F 5, 25 = 10.15, $P < 0.001$). The means for *a* are presented in Fig. 2, together with the individual means for the single drug sessions. Duncan's test on these data established that, with respect to the pooled placebo, ethanol and nitrous oxide increased *a* ($P = 0.05$ and $P = 0.01$, respectively) but amphetamine had no effect ($P > 0.10$). With respect to nitrous oxide alone, nitrous oxide combined with amphetamine decreased *a* ($P < 0.05$) whereas nitrous oxide combined with ethanol increased it ($P = 0.05$). Figure 2 also reveals that the results of the latter condition are virtually identical with what would be predicted on the basis of additivity between nitrous oxide and ethanol since their combined effect is equal to the sum of their separate effects (11). The final point in Fig. 2 is that, with the exception of the additivity results for ethanol, the relationships discussed above are still evident when the individual nitrous oxide results are used for comparison purposes, although they are somewhat distorted by the improvement in performance across drug conditions.

Separate frequency distributions of correct first reaction times were generated for each subject in every condition. Inspection of these distributions revealed no differences between drug conditions as a function of the number of choices. Therefore, the results for two different subjects in the 4-choice condition were chosen as representative and are illustrated in Fig. 3.

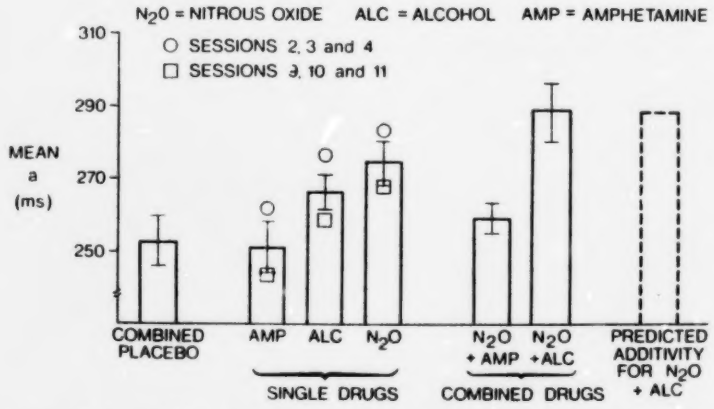

Fig. 2. Means for *a*, the intercept, of the Hick-Hyman function for various experimental conditions based on six subjects. *Bars* represent SEM.

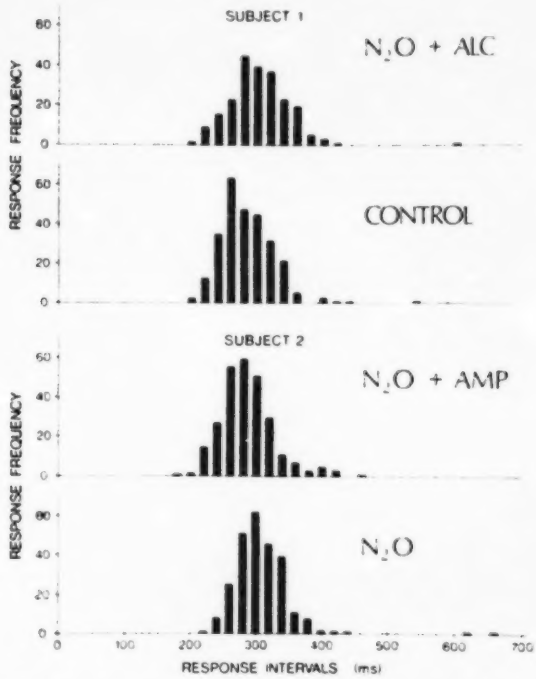

Fig. 3. Representative frequency distributions of 4-choice reaction times for first correct responses, based on a run of 90 s, for two different subjects.

The distributions are positively skewed, but there is little difference in shape across conditions. On the other hand, when compared to the control, subject 1 shows a shift of the whole distribution to the right, toward increased latencies, with the nitrous oxide and ethanol combination. In comparison to nitrous oxide alone, subject 2 shows a shift to the left, toward decreased latencies, when amphetamine is combined with nitrous oxide. The effects of nitrous oxide on the variability of responding was investigated more closely by determining the mean of the SD, summed across subjects, for the first air-breathing control condition (50 ± 7, SEM, ms) as well as the first nitrous oxide alone condition (50 ± 4 ms). These values are identical, indicating that nitrous oxide did not increase the variability of responding. In general, these results suggest that the drugs, either alone or in combination, influence the overall speed of responding in a similar fashion.

To examine errors more closely, the mean response latency for each error, the four responses preceding it and the four following it were calculated for each subject in every session. No differences were noted between drug conditions as a function of the number of choices. Consequently, the 4-choice condition for the first control session, the single drug conditions of sessions 2, 3, and 4, and the combined drug conditions, summed across subjects, were chosen for illustrative purposes. These are illustrated in Fig. 4. The degree of variability in these data is relatively high because the number of errors was relatively low and therefore interpretations must

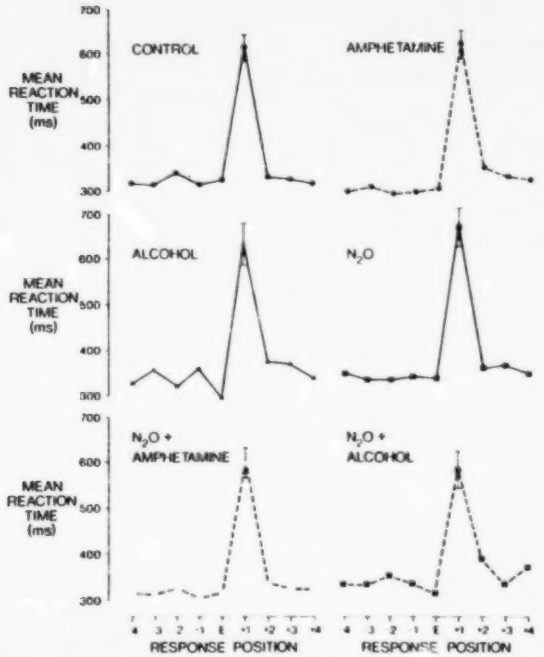

Fig. 4. Representative patterns of 4-choice reaction times around an error (E) based on 6 subjects. *Bars* represent SEM.

be made cautiously. With this in mind, these data clearly show the usual increase in latency on the response immediately after the error. However there are no convincing indications that the pattern differed between conditions. These results suggest that the drugs, either alone or in combination, influenced the pattern of responding around an error in a similar manner.

DISCUSSION

This experiment provides some information on the effects of narcosis on choice reaction time. These data will be considered first before turning to the question of how ethanol and amphetamine influenced narcosis.

First, error rate was controlled at 5% and the subjects had little difficulty in maintaining this rate under narcosis. This is in agreement with a previous study in which the accuracy of movement was found to deteriorate initially under narcosis but could be controlled with training and feedback (12). These results were interpreted as indicating that decreases in accuracy represent a shift in the speed-accuracy trade-off setting, rather than some structural distortion of information processing. The fact that the error rate could be controlled in the present experiment is consistent with this explanation.

Second, the present results shed light on the question of the mom t-to-moment control of responding under narcosis. In a previous study (3), in wl h a 4-choice

response time (reaction time + movement time) task was used with both 35% nitrous oxide and air at 10 atmospheres absolute (ATA), the response distributions showed an overall slowing and the presence of bimodality. It was proposed that the increase in variability under narcosis represented either the disruption of an internal clock or a relaxation of the criterion governing the maintenance of accuracy limits. The former explanation implies that this increase in variability could not be controlled with training, whereas the latter implies that it could. In the present experiment, the frequency distributions of reaction times were also shifted to the right, but variability, as reflected by the SD of the distributions, was unaffected. This result can be interpreted as supporting the explanation that the criterion was relaxed, since it could be argued that maintaining an overall error rate of 5% resulted in the need to control moment-to-moment responding within strict accuracy limits. Another point is that the absence of bimodality suggests that its presence when response time is measured (3) is due to some aspect of movement, possibly anticipatory movements toward unlit buttons that are "pulled" before contact (13).

Two other sets of results from this experiment are consistent with previous research. The finding that the pattern of response latencies around an error was unaffected by narcosis has also been reported for response time (3). This implies that the nature of the cognitive processing involved in correcting an error, as distinct from the speed of processing, remains unchanged under narcosis. The increase in *a*, the intercept, rather than in *b*, the slope, of the Hick-Hyman function representing the relationship between the number of stimulus-response choices and reaction time (10) is the same as that observed previously for various doses of nitrous oxide in a card-sorting task involving 2, 4, 6, and 8 choices (14, Experiment 2). Changes in *a* rather than in *b* have also been found for a number of other tasks, not involving the Hick-Hyman Law, including stimulus brightness with 35% nitrous oxide (3, Experiment 2), stimulus size using air up to 7 ATA (15), and short-term memory set size with the general anesthetic enflurane (16). This change in *a* rather than in *b* has been used to infer that narcosis leads to slowing of the CNS, which is not specific to the information processing stages represented by these tasks (2–4).

Turning to the main purpose of the experiment, the results support the hypothesis that alcohol exacerbates narcosis and amphetamine ameliorates it. Using the pooled nitrous oxide condition as a basis for comparison, it was found that ethanol combined with nitrous oxide increased *a*, the intercept of the Hick-Hyman function, while amphetamine combined with nitrous oxide decreased it. Pooling the nitrous oxide conditions appears to be the most appropriate procedure for comparison purposes because the improvement in *a*, evident in the single drug conditions, was probably also occurring in the combined drug conditions. However, the same pattern of effects emerges, although less clearly, when the individual nitrous oxide conditions are used for comparison purposes. The finding that the combined effects of ethanol and nitrous oxide are additive only holds for the pooled comparison and must be treated cautiously.

It was not possible to determine from this experiment whether the ameliorative effect of amphetamine was additive or synergistic because amphetamine alone had no significant effect on reaction time. This absence of an effect may seem paradoxical, since amphetamine influenced reaction time when combined with nitrous oxide. This can be explained by assuming that amphetamine does not improve reaction time beyond some optimum level of performance but can ameliorate deterioration from

that level. This is consistent with evidence that amphetamine improves reaction time in fatigued and drowsy subjects but often has no effect when they are nonfatigued and alert (9).

Possibly, the effects of ethanol, amphetamine, and nitrous oxide in this experiment can be explained by their influence on different CNS mechanisms, but a more parsimonious explanation is that these drugs affect a common dimension of CNS activity with poles of excitation and depression. This dimension may be viewed as representing the level of arousal. Two arguments can be made for this case. First, the drugs showed a common pattern of effects: (a) error rate could be controlled; (b) the intercept and not the slope of the Hick-Hyman function was affected; (c) the frequency distributions of responses were shifted as a whole with shape unaltered; and (d) the pattern of reaction times around an error was unaltered. Second, ethanol and amphetamine influenced the effect of nitrous oxide in opposite directions, in a manner consistent with the arousal hypothesis.

Finally, an important question is whether these results can be generalized. Present evidence does not contradict the view that the inert gases exert qualitatively identical effects on behavior (4). In particular, it has been demonstrated (3) that the effects of nitrous oxide and hyperbaric air are identical on the response time version of the SCRT task used in the present study. Therefore, these results may be applicable to nitrogen narcosis, but this possibility needs to be verified by further research.

This is Defence and Civil Institute of Environmental Medicine Research Paper 86-P-37.—*Manuscript received for publication October 1985; revision received January 1986.*

Fowler B, Hamilton K, Porlier G. Effets de l'éthanol et de l'amphétamine sur la narcose des gaz inertes chez les humains. Undersea Biomed Res 1986; 13(3):345–354.—Les effets de l'alcool éthylique (1 ml/kg de poids corporel), dextroamphétamine (15 mg), et du protoxide d'azote (20%) sur le temps de réaction furent investigués chez 6 sujets à l'aide d'un test de temps de réaction sérié avec 2, 3, et 4 choix. Chaque drogue fut évaluée séparément et en combinaison avec le protoxide d'azote. Le taux d'erreur fut tenu constant. Ni l'éthanol et le protoxide d'azote et ni l'amphétamine et le protoxide d'azote n'influencèrent la pente de la fonction Hick-Hyman, mais la première combinaison augmenta l'intercepte tandis que la dernière la diminua. Dans l'ensemble, les drogues, soit seules ou combinées, déplacèrent les distributions de fréquences des temps de réaction, plutôt que de modifier soit leurs formes ou l'allure des latences des réponses autour d'une erreur. Ces résultats indiquent que les drogues possèdent un genre d'effets communs sur le temps de réaction et que l'alcool aggrave la narcose alors que l'amphétamine l'améliore. Ceci est interprété comme une évidence supportant l'idée que la narcose produit un ralentissement non spécifique du processus de l'information par une diminution de l'état d'éveil.

narcose — éthanol
protoxide d'azote — amphétamine
temps de réaction au choix

REFERENCES

1. Shilling CW, Werts MF, Schandelmeier NR, eds. The underwater handbook. A guide to physiology and performance for the engineer. New York: Plenum Press, 1977:386–400.
2. Fowler B, Granger S. A theory of inert gas narcosis effects on performance. In: Bachrach AJ, Matzen MM, eds. Underwater physiology VII. Proceedings of the seve[illegible] symposium on underwater physiology. Bethesda: Undersea Medical Society, 1981:403–41[illegible]

3. Fowler B, Granger S, Ackles KN, Holness DE, Wright GR. The effects of inert gas narcosis on certain aspects of serial response time. Ergonomics 1983; 26:1125–1138.
4. Fowler B, Ackles KN, Porlier G. The effects of inert gas narcosis on behavior—a critical review. Undersea Biomed Res 1985; 12:369–402.
5. Thayer RE. Toward a psychological theory of multidimensional activation (arousal). Motiv Emotion 1978; 2:1–34.
6. Vanderwolf CH, Robinson TE. Reticulo-cortical activity and behavior: A critique of the arousal theory and a new synthesis. Behav Brain Sci 1981; 4:459–514.
7. Näätänen R. The inverted-U relationship between activation and performance: A critical review. In: Kornblum S, ed. Attention and performance IV. New York: Academic Press, 1973:155–174.
8. Wesnes K, Warburton DM. Stress and drugs. In: Hockey GRJ, ed. Stress and fatigue in human performance. Chichester, UK: John Wiley, 1983:203–243.
9. Ivy JL. Amphetamines. In: Williams MH, ed. Ergogenic aids in sport. Champaign, IL: Human Kinetics, 1983:101–127.
10. Welford AT. Fundamentals of skill. London: Methuen, 1968.
11. Miller JC, Miller KW. Approaches to the mechanisms of action of general anesthetics. In: Blaschko HKF, ed. Physiological and pharmacological biochemistry. London: Butterworth, 1976:39–76.
12. Fowler B, White PL, Holness DE, Wright GR, Ackles KN. The effects of inert gas narcosis on the speed and accuracy of movement. Ergonomics 1982; 25:203–212.
13. Fowler B, White PL, Wright GR, Ackles KN. The effects of hypoxia on serial response time. Ergonomics 1982; 25:189–201.
14. Berry C, Gelder MG, Summerfield A. Experimental analysis of drug effects on human performance using information theory concepts. Br J Psychol 1965; 56:255–265.
15. Banks WW, Berghage TE, Heaney DM. Visual recognition thresholds in a compressed air environment. Aviat Space Environ Med 1979; 50:1003–1006.
16. Adam N, Collins GI. Search in short-term memory during inhalation of a general anesthetic in man. T-I-T J Life Sci 1977; 7:53–58.